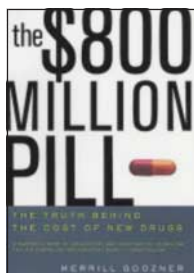


reviews

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The \$800 Million Pill: The Truth Behind the Cost of New Drugs

Merrill Goozner



University of California Press,
\$24.95/£16.95, pp 297
ISBN 0 520 23945 8
Also available as a digital
download
www.ucpress.edu/

Rating: ★★

Two sets of statistics summarise the two main preoccupations of this book.

Firstly, the costs of drug development. The Tufts University Center for the Study of Drug Development calculated that in 2001 the pharmaceutical industry spent \$802m (£446m; €663m) per marketed drug, while the Global Alliance for TB Drug Development thought that a new antituberculosis drug could be developed in the public sector for as little as \$115m to \$240m, conceding that the international nature of the effort required would reduce costs.

The Global Alliance did not take into account the development of me-too drugs, the costs of developing enantiomers—drugs that are mirror images of other drugs—and alternative formulations of established drugs, and the funding of marketing trials, all involving research that Goozner calls “corporate waste.”

The implication is that the industry, motivated by profit, is profligate. But this ignores the benefits of some of this sort of research. For instance, while many individual me-too drugs differ in only small ways from their predecessors, each has unique properties, and the cumulative progress that is made in developing such drugs can lead to important advances.

Witness, for example, the progression pronethalol (1963), propranolol (1964), sotalol (1967), practolol (1969), atenolol (1972), timolol (1973), labetalol (1975), celiprolol (1980), bisoprolol (1984). Between 1963 and 1967, no me-too drugs were produced, but 19 were produced between 1980 and 1984. Yet 70% of the publications on beta blockers listed in PubMed deal with the nine drugs named above. This shows how cumulative advances can come from small serial developments. If the companies that developed the other 44 drugs had known at the start that most of them would fail they would not have developed them;

but prediction is hard, especially of the future.

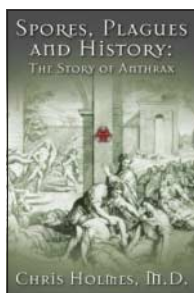
Secondly, Goozner is preoccupied with the ratio of company to public spending. Up to the end of 1996, for example, while total pharmaceutical company spending on AIDS-related research was under \$5bn, the US government spent just under \$10bn. Goozner doesn't tell us that it was ever thus. In 1965, for example, total US federal expenditure on all technological research and development was \$13bn, industrial expenditure \$6.5bn. Goozner does not discuss the sources of this disparity, whether it is a necessary one, and whether we would all gain if the disposition of expenditure was different.

The 1965 figures come from an excellent book called *The Sources of Invention* by the economists John Jewkes, David Sawers, and Richard Stillerman (W W Norton, 1958; 2nd edition, 1968), who consider this disparity and related issues critically and in some detail. Seek a second-hand copy of *The Sources of Invention* (readily available through the usual electronic sources). The book that does for the pharmaceutical industry what Jewkes and his colleagues did for technological innovation has yet to be written.

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Spores, Plagues and History: The Story of Anthrax

Chris Holmes



Durban House, \$15.95,
pp 227
ISBN 1 930754 45 0
www.durbanhouse.com

Rating: ★★★

This book begins dramatically with compelling information about the bioterrorism attack involving anthrax sent through the postal system in the United States in 2001. Holmes describes the patients' cases in great detail, combining medical descriptions (radiological and clinical pictures) with the drama of the

events as they emerged. He then summarises the use of anthrax, as well as other microbes, as agents of bioterrorism and warfare agents. More generally, he discusses epidemics throughout history, both ancient and modern: during the time of Moses and the 10 great plagues of Egypt; the plague of Athens in 430 BC; the Black Death epidemic of the Middle Ages; and the development of “wool sorter's disease” (inhalational anthrax) during the industrial revolution.

Holmes also considers the role and life history of the great pioneers in medicine—Robert Koch and Louis Pasteur—in the discovery of the causes and pathogenesis of anthrax, tuberculosis, cholera, rabies, and other infectious diseases; the development and use of biological weapons in the 20th century by Japan and the former Soviet Union; the American biological weapons programme; the accidental anthrax epidemic at Sverdlovsk in the Ural mountains in 1979; and Saddam Hussein's development of a biological weapons programme in the 1990s and the efforts to curtail and

destroy it. He concludes by reviewing the medical preparedness and preventive capability of the United States in the event of bioterrorism.

The author presents interesting theories relating to major historical events and discusses the role of plagues in these events. He correlates historical evidence with clinical and medical signs and symptoms that substantiate his conclusions. He builds up an intricate body of evidence and conclusions that add a new dimension to history. For example, he suggests that Alexander the Great was intentionally exposed to anthrax and died as a result.

A well written book, it skilfully intertwines medical, journalistic, historical, poetic, and theatrical styles. Holmes uses lay and medical terminology, and his book is suitable for reading by the general public as well as the medical community. The book is educational and entertaining.

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The tabloid fixation on superbugs

“Superbug crisis worse than feared,” “Superbug kills 22 in one hospital in a year,” “Our squalid hospitals: no wonder the MRSA superbug is so rife,” “We find 80 times danger level of MRSA in hospital.” The media in the United Kingdom have developed a fascination for methicillin resistant *Staphylococcus aureus* recently. The *New York Times* was moved to observe that “newspapers around the country have been clamoring to find victims and to publish their sordid stories.” Most articles centre on poor hand hygiene of staff and the state of cleanliness of the hospitals, illustrating the problem with some unfortunate patient’s story. Some even include cases of methicillin sensitive *S aureus* (MSSA), particularly if it happens to involve a minor celebrity.

There is little doubt that MRSA infection can be difficult to treat and may spread easily to some patients. Infections prolong stays in hospital and can increase mortality. The number of lawsuits citing MRSA infection is increasing exponentially. However, MRSA has been a constant problem in many UK hospitals since 1993, so why has attention become so intense now?

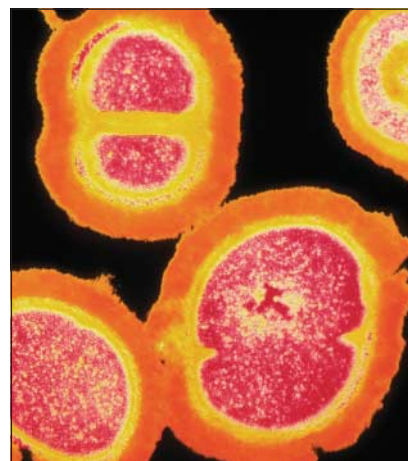
Part of the coverage stemmed from the publication in mid-July of the National Audit Office’s report on hospital acquired infection, which noted disappointing progress since its last report on the subject four years ago. Lack of mandatory surveillance was a major problem. High bed occupancy was common practice in order to meet performance targets but made

separation of elective and emergency patients difficult. The first page of the report gave a map of Europe, derived from a 2002 survey, that showed that the United Kingdom had the highest proportion of methicillin resistance in *S aureus* causing bacteraemia. *S aureus* bacteraemia had increased by 8% since 2001 and MRSA bacteraemia by 5%, representing 7647 cases a year.

A few days ahead of the report the health secretary tried to soften its impact by releasing an outline of his intended measures to combat MRSA. These included installing hotline phones by patients’ beds to alert cleaning staff, publication of infection rates, flying in experts to advise, and asking patients to police the hand hygiene of hospital staff. Some of these ideas attracted angry letters from UK experts and patients’ groups. Then, in response to an MP’s question, the Office of National Statistics released crude data on numbers of deaths in hospital that were possibly related to MRSA, which promptly appeared in the press as a league table. However, the figures took no account of the underlying medical conditions, mix of patients, or the number of patients admitted already carrying the organism. Furthermore, inclusion of MRSA on a certificate very much depends on the interests and diligence of the doctor. Private healthcare companies reported very low rates of MRSA bacteraemia, probably because they have a high proportion of single rooms, so that contact and airborne transmission is reduced. However, NHS consultants observed that the most susceptible patients are usually managed in NHS hospitals and that the capital and staffing costs to provide similar accommodation in NHS hospitals would be immense.

To that extent the coverage was understandable, if lurid at times. However, throughout the early months of this year the main focus had been on poor standards of hospital cleanliness, with MRSA as the benchmark. Undercover reporters were sent to examine hospitals. Bloodstained walls, overflowing clinical waste bins, and a culture of laziness in cleaning staff were frequent complaints, although no analysis was done to establish which failings would be likely to cause infections in patients. Hospital trusts said their buildings were old, cramped, and often had little storage, all complaints familiar to hospital staff. But hospitals need to be kept clean whatever their condition. More investment was needed in providing cleaning services and in refurbishment. Although use of alcohol hand rub was increasing, compliance with hand hygiene remained poor and was worse when staffing levels were low.

More worrying was a string of reports on the activities of an unaccredited laboratory conducting clandestine environmental sampling in hospital entrances, shops, public transport, and food shops. MRSA was apparently found in a high proportion of sites, resulting in sensational headlines and more newspaper sales. Even ticket machines



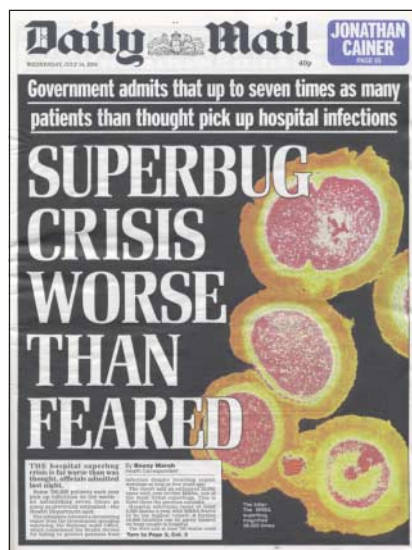
KARI LOUNATMAA/SPFL

The tabloids love MRSA

and escalators in train stations were said to have traces of MRSA greatly exceeding “danger level,” though the reports failed to define what that might be. When some institutions conducted their own tests and found no evidence of MRSA anywhere, the same papers did not question the performance and validation of their own tests or ask for independent review. Publication of scientific results without peer review or opportunity for scientific debate has long been one of the less attractive pastimes of some of the press. A peer reviewed study from St Thomas’ Hospital did appear at this time showing contamination of the hospital environment by MRSA, but in the wards and patient rooms, and it did not examine communal areas.

MRSA is well adapted to causing disease in hospital patients, particularly those with wounds. Infections with MRSA can be more difficult to treat than infections with MSSA but are hardly a new phenomenon. Britain has a particular problem with the organism and needs to move away from a low cost, high turnover ethic in the NHS to an ethic of investing in and allowing time for cleaning. Staffing levels need to rise to allow individuals to practise better hand hygiene. Hospital architects should be trained in infection control. MRSA does contaminate the local environment of hospital patients who carry the organism and may sometimes be further spread by hand after contact with these surfaces. However, even if MRSA exists further afield in the community it is at a low level, and there is no evidence that it causes additional infections. Raising public awareness can be helpful, but the creation of a climate of fear among patients entering hospital is more likely to increase newspaper sales than to provide a solution. Clearly a part of the press considers MRSA to be a useful political stick. Objective reports such as that of the National Audit Office are more helpful to microbiologists at the front line than sensational stories based on questionable results.

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PERSONAL VIEW

The three paradoxes of private medicine

Like many people in Britain I have inherited—and have subsequently nourished—a profound dislike of private medicine. However, it now appears that the reality is much more complicated and disturbing.

We had been told that my daughter would have to wait at least two years to see the consultant as an outpatient, and we felt that this was totally unacceptable. So we made one simple phone call to the private hospital, and she was seen in two weeks.

This much was accomplished without trauma. When we made the appointment it felt like any other—perhaps to see the general practitioner or a school teacher. But the experience began to be qualitatively different when we got there. It began with a feeling of relief that the uncertainty and waiting were over. Then, three things happened that gave me pause for thought.

Firstly, the staff were different. They may have had the same job titles and qualifications as staff in the NHS, they may also have had NHS jobs (the consultant certainly did), but they behaved differently. There was a perception of deference to you, the receptionist was caring, they seemed to have more time, the consultation was less pressured (you know that there is no one waiting outside, so you can take as long as you like). So far, so good. But in each of these apples is a worm. Are they only being nice because I'm paying? If so, what do they say behind my back? Do they think I'm as compromised in this Faustian bargain as they are? Is the consultant being pleasant or oleaginous, altruistic or avaricious?

These issues matter because they go to the heart of the encounter: do I respect this person, and therefore do I trust his advice and actions? This is especially important given the manifest perverse incentives, where every additional action means personal income. When he says, "I can see you for the next appointment on the NHS, but it will be a few months," do I believe him? When he suggests drugs rather than waiting and seeing, could there be ulterior motives? One of the marvels of the NHS is that you can generally trust the motives of the professionals—but here? The result is the first paradox: paying for health care can actually be disempowering.

Then there is the act of paying itself. The private sector recognises the problem here, and its staff try to be very discreet about money. There are several unwritten rules. The consultant is happy to talk about the cost of drugs, but he doesn't mention how much he will charge for his time—and you somehow know not to ask. The secretary

exists for this task, and she delivers the news with a slightly shamefaced and conspiratorial discretion and understanding, laying great emphasis on the fact that the debit will not appear on your credit card statement for 14 to 21 days.

This nicely preserves the hierarchy and the professional ethos; it's almost as though you weren't really paying for the guy's time at all. The hospital bill is settled in a rather pleasant cubicle called "Cashier," where a third party (unconnected with the clinical element) handles the transaction, and the credit card machine is carefully hidden behind the computer. So, the second paradox is that private medicine does not actually seem to cost anything—or, at least, one can suspend one's disbelief for the duration of the encounter.

Finally, private medicine seduces. Just as inevitably as Faust faced Mephistopheles, the erstwhile socialist private patient sells his soul. The first time you realise this has happened is when you find yourself avoiding telling friends and colleagues that you have actually "gone private." And then when you go to your GP to collect the results of the blood test so that you can take them to the

next private consultation, you find yourself talking in an undertone to the receptionist so that no one else knows you are "private," and you avoid looking at the poor sods in the waiting room who perhaps are only there because they could not afford what you could. No wonder the whole transaction is termed private. Would you want it publicly known?

So, paradox number three: instead of the joy of clinical resolution, you are left with a tainted feeling of shameful compromise and guilt. And now that you have done it once, you know that you are more likely to do it the next time. But worse: while you would rather keep the whole episode "private," you would vigorously defend your actions if you had to. It feels wrong, but you'd do it again.

And so it goes on, patient after patient, year after year. But don't expect me to endorse private medicine as a concept. I still think it stinks.

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We welcome submissions for the personal view section. These should be no more than 850 words and should be sent electronically via our website. For information on how to submit a personal view online, see <http://bmj.com/cgi/content/full/325/7360/DC1/1>

SOUNDINGS

Under the Tuscan sun

The heat in Tuscany is quite unlike that in England. In England, no matter how hot the day, there is always that hint of a chill—the merest echo that warns that summer is short and that winter, loaded with the passage of time, is not far away. Here the heat is like a blanket. It wraps away the anxieties of life in a cocoon of enforced idleness and fatigue.

Holidays do not come naturally to me and I have to work at them. I need to consciously step sideways out of time, leaving the banalities of life at the airport. It is like a meditation. Reading by the pool is not the purposeful reading of real time. It is the adrift reading of childhood. Like the leisured class of earlier generations, you can drift in and out of half finished conversations and ideas.

The guidebook falls open so you read it because it is there—Lorenzo de Medici was a tolerant leader, a scholar, civilised; Girolamo Savonarola, his enemy, was a religious bigot, a bad guy.

In the brief cool of this morning we wandered into the village. The frescoes in the church, now faded and patched with brown plaster, capture that time when Europe, under the patronage of men like Lorenzo, was tentatively emerging from a thousand years of bigotry and intolerance. The frescoes, like the renaissance they herald, look fragile.

The tiny village was also the home of a Franciscan monk called Pacioli. Pacioli, again under the benign patronage of Lorenzo, restarted European mathematics in 1494 with a book that introduced the Hindu-Arabic place-number system.

It is sobering to think that European learning had effectively ceased in the sixth century when the Emperor Justinian I closed Plato's Athenian academy because he considered it pagan. For a thousand years it was the Islamic world that held the torch of learning and tolerance.

The outside world briefly re-entered our holiday when the cultured owner of our villa returned from a business trip to Istanbul. The hotel next to his was bombed with three dead. Civilisation, like the English summer, is fragile.

So what does the guidebook tell me of Savonarola? Not a lot. But you get the impression that, like today's religious fundamentalists, he didn't really see the funny side of life. Maybe he should have taken more holidays.

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